I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450, ON THE DATE INDICATED BELOW.

BY: _____ Date: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of: Winston T. K. Cheng et al.	:	
Conf No: 8832	:	Group Art Unit: 1632
Appln. No.: 10/820,777	:	Examiner: Michael C. Wilson
Filing Date: April 9, 2004	:	Attorney Docket No.: 683884-2US (CCM0002US)

Title: METHOD FOR PRODUCING BIOLOGICALLY ACTIVE HUMAN FACTOR VIII IN THE MILK OF TRANSGENIC ANIMALS DRIVEN BY MAMMARY-SPECIFIC EXPRESSION CASSETTES

DECLARATION OF CHUAN-MU CHEN UNDER 37 C.F.R. § 1.132

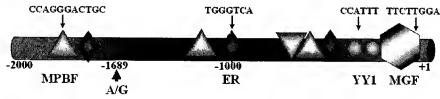
I, Chuan-Mu Chen, hereby declare as follows,

1. I am a joint inventor of the patent application No. 10/820,777 (hereinafter '777 application). I am employed as a Molecular Embryologist and a Professor of the Department of Life Sciences and Institute of Biomedicine at the Chung Hsing University. My current research focuses on the area of gene regulation studies in preimplantation embryo genomes and tissue-specific gene expressions of transgenic animal generations for bio-pharmaceutical productions. I am also interested in research in elucidating the alternative epigenetic modification of DNA methylation change in cancer biology and developmental biology. I have published more than 35 papers and 13 patent applications in embryonic research and cancer research fields (see Annex I provided in my Declaration filed July 17, 2006, in the '777 application). I have been a reviewer for the Taiwan Government National Science Council (NSC) Research Program since 1998, and also an overseas reviewer for the Research Grants Council (RGC) of Hong Kong since 2002. Together with a leading Taiwan transgenic cloned animal research team, I have earned an honor of the Taiwan President Agriculture Innovation Award in 2006.

2. In light of my background and my professional experience, I consider myself and expert and am considered by others as an expert in the fields of research and science mentioned above. As a result, I am qualified to clarify the non-obviousness of the invention claimed in the '777 application. I have reviewed and understand the claims of the '777 application being submitted with this Declaration.

3. The recombinant human FVIII (rFVIII) and B-domain deleted FVIII protein expression in the milk of transgenic mice, goats and pigs, would also be successfully expressed in the milk of transgenic cows. Several original designs of mammary gland-expressing cassette for exogenic human FVIII gene regulationhave been made in this invention. The advantages and features of the rFVIII production in the milk of transgenic animals according to the invention comprise:

(A) This is the first identification of the **stringent lactating-specific regulation sequence (2.0-kb) of alpha-lactalbumin gene from a high milk-producing Holstein cow** (as described in the "Transgenesis Constructions" section at pages 11-12 of the specification of the '777 application) with essentially transcriptional binding motifs, such as MPBF, ERRE, YY1, and MGF motifs as shown in the following Supplement Figure 1:



Supplement Figure 1. The map and structure of bovine alpha-lactalbumin (αLA) 2.0-kb promoter sequence. The essentially transcriptional binding motifs, such as MPBF, ERRE, YY1, and MGF motifs are also shown in the promoter region.

(B) The expression system provided in the '777 application has an **extremely high secretion signaling for leading rFVIII protein secreted into mammary alveoli**, by construction of **artificial alpha-lactalbumin 19-amono acid signal peptide sequences (SEQ ID NOs:1 and 13) or an artificial alpha-S1-casein 15-amino acid signal peptide sequences**

(SEQ ID NOs:2 and 14) to replace the intrinsic 19-amino acid signal peptide signal sequence of the human FVIII gene;

(C) According to the invention disclosed and claimed in the '777 application, **successful germline-transmitted transgenic mice, goats and pigs harboring B-domain deleted rFVIII (SEQ ID NO:15) in their genomes** have been generated, which guaranteed a high rFVIII protein synthesis in the lactating mammary gland of transgenic animals; and

(D) The invention disclosed and claimed in the '777 application provides a **highly secreted efficiency of rFVIII protein in the milk of transgenic animals with 250-fold (> 50 μg/mL) more concentration** than that of normal human plasma (0.2 μg/mL), and **the clotting activity also reached a level of 25-fold** higher than that of normal human plasma. These results are superior than those previous reports on hFVIII production in transgenic animal systems.

(E) *In vitro* results can not always be reproduced *in vivo*. None of the references cited in the Office Action or combination teaches or suggests the production of recombinant FVIII with a relative high yield by the transgenic animal systems including (1) B-domain deleted rFVIII cDNA construct combination with (2) 2.0-kb intact αLA promoter and (3) mammary gland-specific signal peptide.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the '777 Application or any patent issued thereon.

Date: **June, 29, 2007**

Chuan-Mu Chen